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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/595,682	06/16/2000	Mary K. Danks	SJ-0005	1625

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1633	14

DATE MAILED: 01/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/595,682	DANKS ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-11,15-17 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-21 are pending in the application.

Election/Restrictions

Applicant's election with traverse of claims 12-14 and 18 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that there is no undue burden on Examiner to search the entire application. Applicants further argue that all the groups contain claims with the same elements, namely, an isolated polynucleotide encoding a carboxylesterase of metabolizing a chemotherapeutic prodrug and inactive metabolites.

This is not found persuasive because groups I-VII are patentably distinct for the same reasons of record as set forth in the prior office action mailed on 10/2/01. Although each group contains claims with the same elements, however, the search is not co-extensive. Therefore, it would be a burden to search all the groups.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 12-14 and 18 are currently under examination on merits. Claims 1-11, 15-17 and 19-21 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

Claims 12-14 and 18 are objected to as being dependent upon non-elected base claims (1 and 8). But for the purpose of examination, the limitations of claims 1 and 8 will be read into claims 12-14. Applicant is advised to rewrite claims 12 and 18 in independent form including all of the limitations of (non-elected) base claims (1 and 8).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method of inhibiting tumor growth in a patient comprising administering to the patient a composition comprising a polynucleotide encoding a carboxylesterase (CE) and a tumor-specific promoter; and APC, an inactive metabolic end product of CPT-11 (a chemotherapeutic prodrug). The specification discloses the purification and cloning of a rabbit CE that is effective in converting CPT-11 to SN-38, an active metabolite of CPT-11 (see page 32, example 2). The specification further discloses that transfecting tumor cells with a construct encoding the rabbit liver CE sensitizes the cells to the cytotoxic effect of CPT-11 both in culture and in xenograft implanted in SCID mice (see page 37 example 7, page 39, example 9). The specification also disclose that rabbit liver CE is able to convert APC to SN-38 (see page 38, example 8).

At the time of filing, the relevant art considered efficient delivery systems are essential for such genetic prodrug activation therapy as well as for other types of gene therapy (see Rigg and Sikora, page 364, 1st column, line 5-6). However, the relevant art also considered gene

therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein has not been developed. Crystal (1995) states that human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy (abstract) and that the human transfers had been plagued with inconsistent results (page 409, 1st column, 2nd paragraph, lines 1-4) Crystal also recites: "Humans are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials. (page 409, "What are the obstacles to successful human gene transfer paragraph"). Verma et al., (1997) states "there is still no single outcome that we can point to as a success story" (See Gene Therapy Promises, problems and Prospects, Nature, Vol. 389, pg. 239, col. 1). Anderson (1998) also states that there have been conflicting reports regarding the immunogenicity, stability of gene expression, and persistence in vivo of gutless vectors, and these properties may differ depending on exact vector design, the tissue type that the vector is introduced into, and the nature of transgene insert (Vectors based on DNA viruses, See page 27-28, column 7). Walther and Stein (2000) indicate in the review article "the majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy (See page 267, discussion column). Mountain (2000) recites in the review article "Each gene transfer system has its own combination of advantages and limitations" (See Gene Therapy: the first decade, col. 5, pg. 121). Riggs and Sikora also discuss the advantages and disadvantages of each vector system and point out there is no ideal system at present (see page 364, table 2 and 3, 2nd column, 3rd paragraph). Thus to overcome these teachings in the art, the specification would need to supply

direct, correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective to sensitize tumor cells in a patient to the cytotoxic effect of APC and thus inhibiting tumor cell growth in the patient. In addition to the above technical difficulties, the prior art also indicate that not all CE can effectively convert APC to SN-38, for example, human liver CE (see Rivory et al. 1996, page 3693, 1st column, 3rd paragraph, lines 1-2). Thus the specification also needs to provide guidance to use CE regardless its source to sensitize cells to cytotoxic effect of APC.

The amount of guidance presented in the specification is very limited. The specification discloses transfection of CE into rh30 in vitro and followed by selection of G418 to ensure cells expressing CE. The specification also disclose these cells expressing CE are subsequently introduced into SCID mice. The specification does not teach the route of delivery of the composition comprising the polynucleotide and APC to inhibit tumor growth in a patient. The specification also fails to teach the effective amount of both the polynucleotide construct and APC to inhibit tumor growth in a patient. The specification does not disclose any CE other than the rabbit liver CE is efficient in converting APC to SN-38 in culture.

The breath of the claim is very broad because it is drawn to a method of inhibiting tumor growth by administering APC and a construct encoding a CE regardless of the source of CE, tumor origin, routes of delivery and effective dosage. However, it is unpredictable whether tumor in a patient would express effective amount of CE to sensitize tumor cells to cytotoxic effect of APC because the specification fails to disclose an effective delivery method to ensure expression of CE in tumor cells in a patient. In addition, tumor growth subcutaneously in a SCID mouse is different from tumor growth in a natural environment in a patient. Therefore, the

inhibition of tumor growth in a SCID mouse is unpredictable for the success of inhibition of tumor growth in a patient. To attempt to practice the invention of inhibiting one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art, does not teach a method of delivering effective amount of APC and polynucleotide encoding CE to inhibit tumor growth. Therefore, one skilled in the art would require in undue experimentation in order to determine 1) which CE is effective in converting APC to SN-38; 2) the route of deliver to each tumor type; 3) the effective amount to sensitize tumors to cytotoxic effect of APC.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: wherein expression of the carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic agent.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and

useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 12-14 and 18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 11-13 and 17 of copending Application No. 09/622568. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
January 28, 2002

REMY YUCEL, PH.D
PRIMARY EXAMINER